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Factors associated with hospital death in patients who died from liver disease: A national population-based study in England

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Abstract

Background

Liver disease is a major cause of mortality with high hospital death and disproportionately affects people under 65. This study aims to examine the place of death and factors associated with hospital death for those who died from liver disease.

Methods

Population-based observational study using the National Death Registration Database from the Office for National Statistics, 2001–2014. All non-accidental adult deaths (hospital and non-hospital) from liver disease in England were included. Explanatory variables were underlying cause of death, contributory causes of death (number and specific causes), age at death, sex, marital status, year of death, index of multiple deprivation, rural/urban settlement and residential region. Modified Poisson regression models were applied to evaluate the strength of association between hospital death and explanatory variables using adjusted prevalence ratio (PR).

Findings

A total of 135,953 decedents were included, and 56,065 (41·2%) of them died from alcoholic liver disease. The annual deaths from liver disease increased

from 7,811 in 2001 to 11,017 in 2014. Hospital was the main place of death (66·9%, 95% confidence interval 66.6%–67.1%) for patients who died from liver disease. The proportion of hospital deaths reduced from 71·5% (2001) to 60·0% (2014). After adjusting sociodemographic factors, patients who died from alcoholic liver disease had the highest chance of hospital death; those from liver cancer were less likely to die in hospital (PR 0·61, 95% confidence interval [95%CI] 0·60–0·61, reference: alcoholic liver disease). Those with more contributory causes of death (PR 1·45, 95%CI 1·42–1·47, 4+ versus 0) were more likely to die in hospital. Patients with sepsis (PR 1·24, 95%CI 1·23–1·25), hepatorenal syndrome (PR 1·22, 95%CI 1·21–1·22), and peritonitis (PR 1·18, 95%CI 1·17–1·20) had higher, and those with alcohol related disorders (PR 0·67, 95%CI 0·66–0·69) had lower chances of hospital death, respectively.

Interpretation

The annual deaths from liver disease increased steadily in England, and alcoholic liver disease was the commonest underlying cause of death. Patients with sepsis, hepatorenal syndrome, or peritonitis were associated with high hospital death, which warrants further investigation. The reasons for the disproportionately low hospital death in patients with alcohol related disorders

need to be explored. There is a dire need for prevention strategies as well as end of life care services to prevent and tackle harms from liver disease.

Funding

NIHR HS&DR programme, CLAHRC South London

Keywords

Liver disease; hospital death; cause of death; end of life care; alcoholic liver disease; sepsis; hepatorenal syndrome; alcohol related disorders

Research in context

Evidence before this study

Liver disease is a common cause of mortality, and the number of people who died from liver disease in the under 65s in UK is still on the increase. However, there is a lack of information about the place of death and factors associated with hospital death for those who died from liver disease in the UK.

Added value of this study

This population-based observational study included a total of 135,953 decedents in England who died from liver disease from the Office for National Statistics, 2001–2014. The commonest underlying cause of death was

alcoholic liver disease. Hospital was the main place of death for patients who died from liver disease. Patients who died from alcoholic liver disease had the highest chance of hospital death. Those with more contributory causes of death were more likely to die in hospital. Patients with sepsis, hepatorenal syndrome, and peritonitis had higher, and those with alcohol related disorders had lower chances of hospital death, respectively.

Implications of all the available evidence

Our study provides a good reference for developing tailored care services for people dying from liver disease. Among the whole study population, those who were with sepsis, hepatorenal syndrome, or peritonitis were associated with high hospital death, which warrants further investigation. The reasons for the disproportionately low hospital death in patients with alcohol related disorders need to be explored. There is a dire need for prevention strategies as well as end of life care services to prevent and tackle harms from liver disease.

Background

Liver disease is a common cause of mortality, accounting for 2% of all deaths worldwide according to a global estimate in 2010 (1, 2). In Europe, liver disease is the seventh leading cause of death (3). In the United States, the percentage of those who died from chronic liver disease, cirrhosis, and liver cancer was 2·4% in 2014 (4, 5). Similarly, about 2% of deaths in the United Kingdom (UK) were from a liver disease (6, 7). In the UK, liver disease is currently the 5th most common cause of death in those under 65 years of age, and the number of people who die from end-stage liver disease is still increasing (8). Compared to other organ failure or terminal illness, liver disease disproportionately affects people under 65 years old, hence becoming one of the largest causes of premature mortality (7, 8).

While deaths from liver disease have been decreasing in other European countries, the number of people who died from liver disease in the under 65s in UK is still on the increase (8). It reveals an urgent need to gather more evidence and to take actions against liver disease (9-11). Furthermore, the National End of Life Care Programme in the UK (12, 13) has successfully shifted the place of death, a common population-based marker of care quality, of patients with

cancer from hospitals to people's homes gradually since 2005 (14-16). However, whether the policy changed the care for those dying from liver disease remains unexplored. Lastly, patients dying from liver disease are likely to have specific end of life care needs (7), yet there is a lack of information about the last days of life of these patients and what they die from. Given the strength in nationwide coverage and data accuracy, the death registration data from the Office for National Statistics (ONS) has been well utilised in analysing place of death and its associated factors (14, 17-20). In addition, contributory causes of death from ONS data, which can be seen as complications or comorbidities contributing to a patient's death, provide important contextual information of patients who die from liver disease.

The aim of this study is to examine the place of death and factors associated with hospital death for those who died from liver disease in England, in the context of their socio-demographic characteristics.

Methods

Study design and setting

A population-based observational study in England, 2001–2014.

Data source

The ONS collected data from all death registrations in England, which included decedents' age of death, sex, marital status, residential region, place and year of death, underlying and contributory causes of death, recorded using the 10th edition of International Classification of Diseases (ICD-10) codes. The ONS death registration database was linked with area level indices of multiple deprivation (IMD), which is the official measure of relative deprivation for small areas in England. The IMD combines seven domains of deprivation using the following weights: income, employment, health deprivation and disability, education skills and training, barriers to housing and services, crime, and living environment (21, 22). The unit for IMD calculation is the lower layer super output area (LSOA), which is a low-level geographic area designed for reporting small area statistics. In England, there were 32,482 LSOAs in 2001 and 32,844 LSOAs in 2011 according to the census data. All LSOAs were grouped into quintiles based on the rank of their IMD scores (22, 23).

Study population

All non-accidental adult decedents (>=18-year-old) with liver disease as the underlying cause of death between 2001 and 2014 in England were included for this study. The definition of liver disease underlying causes of death by ICD-10 codes is: alcoholic liver disease (K70), fatty liver disease (K760), viral liver disease (B15–B19), other chronic liver disease (I81, I85, K71–K75, K761–K769, K77), and liver cancer (C22) (7). Disorders of gallbladder, biliary tract and pancreas (K80–K87), though likely to present with abnormal liver function test or jaundice, were not considered because this group were too broad to be discerned if the disorder was truly related to liver (7).

Variables

The study outcome was hospital death, inclusive of all deaths in NHS and non-NHS hospitals. Non-hospital deaths were categorised into 4 groups: home, hospice, care home (including nursing home, residential home, and care home), and elsewhere. The main explanatory variables were underlying cause of death (alcoholic liver disease, fatty liver disease, viral liver disease, other chronic liver disease, and liver cancer), contributory causes of death – number & specific cause of death. Number of contributory causes was grouped into 5 groups: 0, 1, 2, 3, 4+ (4 or more). We planned to extract six liver disease related

complications, including esophageal varices, hepatic encephalopathy, spontaneous bacterial peritonitis, ascites, hepatorenal syndrome, and hepatopulmonary syndrome (24). However, hepatic encephalopathy was not clearly defined in ICD-10, so we applied encephalopathy (G93.4) as a surrogate for hepatic encephalopathy. In addition, we found there was no record of spontaneous bacterial peritonitis (ICD-10: K65.5) in the database, so we broadened the code to K65 (peritonitis) as a surrogate for spontaneous bacterial peritonitis. Chronic comorbidities were collected with reference to the Charlson comorbidity index, inclusive of cardiovascular disease (acute myocardial infarction, congestive heart failure, and peripheral vascular disease), neurological conditions (cerebral vascular disease and paraplegia), dementia, pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes mellitus (diabetes and related complications), renal disease, and non-liver or metastatic cancer (25, 26). We explored the database and identified other 3 most frequently reported contributory causes of death: sepsis (A41), influenza and pneumonia (J09–J18), and alcohol related disorders (F10).

The contextual socio-demographic variables included: age of death (18–34, 35–44, 45–54, 55–64, 65–74, 75–84, 85+), sex (male, female), marital status

(married, single, widowed or widow from civil partnership, divorced or separated or dissolved civil partnership, and unknown or not stated), year of death (2001–2004, 2005–2008, 2009–2014), IMD quintiles (1–most deprived to 5–least deprived), settlement (urban, rural), and residential region (London, South East, South West, East of England, East Midlands, West Midlands, Yorkshire and The Humber, North East, North West). We analysed age as an ordered categorical variable rather than a continuous variable to facilitate interpretation and comparison with other studies. The year of death was divided into 3 intervals based on the launch, implementation, and roll-out of several national initiatives for improving end-of-life care in the UK. The 3 intervals were: 2001–2004 (pre-strategy), 2005–2008 (strategy launch & intensification phase), and 2009–2014 (post-strategy) (12, 13). We used IMD 2004, IMD 2007 and IMD 2010 to map the residential area-based deprivation of the decedents for the period 2001–2004, 2005–2007 and 2008–2014 respectively. The rural/urban settlement was classified using 2001 Census data for those who died between 2001 and 2010, and 2011 Census data for those who died between 2011 and 2014.

Statistical analysis

Variables in the study were described primarily as categorical data using count and percentage. Bivariate analyses were performed to check if there was an association between each explanatory variable and hospital death. The statistical significance was assessed using the chi-squared test. Modified Poisson regression models with robust variance were applied to evaluate the independent association between hospital death and potential explanatory variables, and only those which were statistically significant in bivariate analysis ($p<0{\cdot}05$) were included in the multivariate modelling. The strength of association was measured using prevalence ratio (PR), which is a measure of relative risk, estimated from multivariate models. In this way, we avoided the overestimation of association caused by using odds ratio (27, 28). Potential interaction between variables were explored and tested, and sensitivity analysis was carried out by running separate models omitting one of the concerned variables or taking interactions into consideration. In addition, we plotted the proportion of hospital deaths by year, stratified by underlying cause of death, numbers of contributory cause of death, and other explanatory variables as appropriate. Stata/SE 14 (STATA, College Station, TX) was used for all analyses.

Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HS&DR programme, NIHR, NHS, or the Department of Health. No author was paid to write this article by a pharmaceutical company or other agency. All authors (JKP, IJH, WG) had full access to the raw data in the study. The corresponding author (JKP) had full access to all of the data and the final responsibility to submit for publication.

Results

Between 2001 and 2014 in England, a total of 135,953 adults died from liver disease, representing 2·1% of the total 6,368,760 non-accidental deaths during this period. Among them, 90,921 (66·9%, 95% confidence interval [CI] 66.6%–67.1%) died in hospital, while the other 45,032 (33.1%, 95% CI 32.9%–33.4%) died in a non-hospital setting (home [21·9%], hospice ([5·5%]), care home ([4·3%]), and elsewhere [1·3%]) (Table 1). The annual deaths from liver disease increased steadily from 7,811 in 2001 to 11,017 in 2014 (Figure 1). The proportion of hospital death was stable initially (71·5% in 2001) and then

decreased constantly after 2004/2005 following the national policies of improving end of life care and facilitating home death (in 2014: 60·0%, see Figure 1). There were no missing data in all variables except marital status. The marital status of 1,995 (1.5%) decedents was missing and was categorized as “unknown or not stated”. We analysed them as a category rather than deleting them.

The socioeconomic characteristics of the study population are shown in Table 1. The mean age of death was 62·8 (standard deviation (SD) 14·6). There were more men (61·5%) than women (38·5%). Two fifth of the decedents were married (42·7%), followed by divorced (or separated or dissolved civil partnership, 20·2%), single or widowed (18·0% each), and unknown or not-stated (1·5%). There were relatively more decedents from deprived areas. Those who were classified as the most deprived (IMD quintile 1) and the least deprived (IMD quintile 5) accounted for 30·2% and 13·4%, respectively.

The clinical characteristics of the study population are shown in Table 2. 56,065 (41·2%) decedents died from alcoholic liver disease, followed by liver cancer (29·0%), other chronic disease (24·7%), fatty liver disease (3·0%), and viral

liver disease (2·1%). Those who had more contributory causes of death were more likely to die in the hospital, ranging from 50·7% (number of contributory causes of death: 0) to 83·5% (number of contributory causes of death: 4 or more). The most frequent contributory cause of death was influenza and pneumonia (12·7%), followed by esophageal varices (7·0%), cardiovascular disease (6·9%), and cancer (non-liver or metastatic, 6·7%).

Results of multivariate analysis for factors associated with hospital death are presented in Table 3. Increased age (55 years or above) and female sex were associated with a higher chance of hospital death. Those who were not married, died in 2005 – 2008 or 2009 – 2014, lived in a rural settlement, and were less deprived were less likely to die in hospital. The decedents had a lower chance of hospital death if they didn't live in London.

The underlying cause of death was also associated with hospital death (Table 3). Compared to those who died from alcoholic liver disease, viral liver disease (adjusted PR 0·96, 95% confidence interval 0·95–0·98) and other chronic liver disease (PR 0·85, 0·84–0·86) were associated with slightly fewer hospital

deaths, although this was a larger degree for those who died from fatty liver disease (PR 0·52, 0·50–0·54) and liver cancer (PR 0·61, 0·60–0·61).

The association between contributory causes of death and hospital death is presented in Table 3. There was a significant association between the number of contributory causes of death and hospital death, and a dose-response relationship was noted. Compared to those who had no contributory cause of death, the PRs of hospital death in decedents with 1, 2, 3, and 4+ medical conditions were 1.20 (1·18–1·21), 1·24 (1·22–1·26), 1·32 (1·31–1·34), and 1.45 (1·42–1·47). Those who had sepsis (PR 1·24, 1·23–1·25), hepatorenal syndrome (PR 1·22, 1·21–1·22), and peritonitis (PR 1·18, 1·17–1·20) were more likely to die in hospital. On the contrary, decedents with alcohol related disorders (PR 0·67, 0·66–0·69), dementia (PR 0·77, 0·73–0·82), and non-liver or metastatic cancer (PR 0·80, 0·78–0·81) had a lower chance of hospital death.

Figure 2 demonstrates the time trend of the proportion of hospital death stratified by underlying cause of death, number of contributory causes of death, and the selected contributory cause of death. A markedly increasing trend of

hospital death in patients with fatty liver disease was noted (from 24·3% in 2001 to 53·8% in 2014), while those who died from liver cancer had a persistently low and decreasing percentage of hospital death. For those who had no contributory cause of death, hospital death markedly decreased following the plateau in 2001–2005. In contrast, those who had 4 or more contributory causes of death were still highly likely to die in hospital. The dose-response relationship became more pronounced over these years. The presence of sepsis, hepatorenal syndrome, and peritonitis was individually associated with consistently high hospital deaths (all greater than 90% during 2001–2014). For those with alcoholic liver disease as the underlying cause of death, alcohol related disorders played an important role in place of death. The chance of hospital death was significantly lower if they had these kinds of mental or behavioural disorders as their contributory cause of death.

Discussion

To our knowledge, this is the first population-based study assessing hospital death and its determinants, particularly the underlying and contributory causes of death, in liver disease. Hospital was the most common place of death for patients who died from liver disease. The number of contributory causes of

death was independently associated with higher hospital deaths. Patients who died with sepsis, hepatorenal syndrome, or peritonitis had an increased chance of hospital death, whilst those with alcohol related disorders, dementia, non-liver or metastatic cancer had a lower chance of hospital death.

Our study revealed the annual deaths from liver disease increased markedly in England, and alcoholic use is the leading factor for death in this population, which is consistent with previous studies (7, 9, 29, 30). Globally, alcohol plays an important role in global disease burden and results in tremendous health loss (30-33). It is crucial to reduce overall alcohol consumption in both population and individual level (9, 31, 34, 35). While looking into the evolution or trend between 2001 and 2014, some information is worth being noted (see appendix table and figures). Firstly, those who died from liver cancer doubled during this period, which indicated the importance of prevention and early detection of liver cancer. And as a result, the age of death increased simultaneously because the mean age of death of those who died from liver cancer was 72.3-year-old, which is higher than those who died from alcoholic liver disease (mean 54.8-year-old), fatty liver disease (mean 57.7-year-old), viral liver disease (mean 58.7-year-old), and other chronic liver disease (mean

65.8-year-old). Secondly, the deaths increased in both male and female sex, and female decedents accounted for 38 – 39% constantly during these years. Thirdly, considering residential region, a marked increase was noted in East Midlands (66%) and East of England (65%) (compared 2014 to 2001), while the increase in London was just about 5%. The ecological effect requires exploration.

Though rarely studied before, the information on contributory causes of death of patients dying from liver disease is valuable and can help us understand more about the medical problems that these decedents were facing or that initiated their end of life journey. Accordingly, how to deal with these problems properly becomes important, especially while the policy is committed to help these patients be cared for or to die in the place they prefer. At this point, collaboration between general practitioners, hepatologists, transplantation teams, and specialist palliative care is vital (11, 36-39). In addition, healthcare professionals can utilise these clinical and socioeconomic factors to identify those who are at a higher risk of hospital death and provide appropriate care and timely intervention. However, for each individual patient, “hospital death” itself doesn’t necessarily imply a “good” or “bad” outcome, or “appropriate” or

“not appropriate” care. On the one hand, if the patients choose to die at home, healthcare professionals need to address their needs and try to accomplish their wishes. On the other hand, if the medical problems need to be treated in a hospital setting, considering the best interest of these patients, they should have the opportunities to be cared for and treated in hospital, no matter if they eventually die in the hospital.

Among the contributory causes of death associated with a higher risk of hospital death, infection (including sepsis, peritonitis, influenza and pneumonia) was a key factor. According to previous studies, sepsis was the most common reason for terminal hospitalisations in patients with decompensated liver disease (40). In addition, cirrhosis itself was strongly associated with increased risk of sepsis, sepsis-related mortality, acute respiratory failure, and acute respiratory failure-related mortality (41). This may be because patients with cirrhosis are more susceptible to infection owing to immunologic deficits (42, 43). While infection is seen as a common pathway leading to death, it does not necessarily mean that nothing can be done to improve the care for patients with advanced liver disease. For example, good infection control and judicious use of invasive

interventions in these patients may help to reduce the risk of secondary infection during their hospitalisations (42).

Renal failure (hepatorenal syndrome and chronic renal disease) was also a key factor associated with higher hospital deaths in our study, which is consistent with the result of a study of medical intensive care unit mortality in cirrhotic patients (44). Hepatorenal syndrome is a major complication resulting in renal failure in patients with advanced liver disease, which is defined as the end stage of the reductions in renal perfusion owing to severe hepatic injury (45-47). The prognosis of hepatorenal syndrome is poor, and many patients die several weeks after its onset if there is no adequate treatment (48). Notably, a recent study in Korea compared the causes of in-hospital death in patients with end-stage liver disease between 2002 and 2011. During these years, some of the complications caused by end-stage liver disease had been better treated and were less likely to cause in-hospital death, such as: variceal bleeding, hepatic encephalopathy, ascites, and spontaneous bacterial peritonitis. However, hepatorenal syndrome was still difficult to be treated and accounted for 34.7% of the causes of in-hospital death in 2011 (16·9% in 2002) (49). As illustrated in our study, those who had hepatorenal syndrome as their contributory cause

of death were constantly and highly likely (>90%) to die in hospital over this 14-year period. So far, hepatorenal syndrome is still a challenge in the health care for patients with advanced liver disease.

Patients with non-liver or metastatic cancer and dementia as their contributory causes of death had a markedly lower chance of hospital death in our study. It is not surprising that non-liver or metastatic cancer was associated with a lower chance to die in hospital, given that the palliative care services for patients with cancer are more established than for those patients with non-cancer conditions (12, 13). Among all decedents who had non-liver or metastatic cancer as their contributory cause of death in our dataset, 46·9% died in the hospital, followed by home (30·5%) and hospice (12·9%). The results were similar to a previous population-based study focusing on place of cancer death in England (14). It is also reasonable that dementia was associated with lower hospital death in England, since patients with dementia in England were more likely to die in care homes rather than hospitals. According to a population-based study of 388,899 decedents with dementia in England, 55·3% of them died in care homes, and 39·6% of them died in hospitals (19). So, if patients died from liver disease

cormobid with dementia, they were less likely to die in hospital compared to those without dementia in England.

A noteworthy finding was the disproportionately low hospital deaths in patients with alcohol related disorders. Alcohol related disorders, by definition, are disorders related to or resulting from abuse or misuse of alcohol, which are classified in the group of mental and behavioural disorders due to psychoactive substance use. Alcohol related disorders are presented with one or mixed types of the following clinical conditions, inclusive of acute intoxication, harmful use, dependence syndrome, withdrawal state (with or without delirium), psychotic disorder, amnesic syndrome, residual and late-onset psychotic disorder, and other mental and behavioural disorders (50). Patients with alcohol related disorders may also use more than one psychoactive substance, which complicates the illness and makes the health care more challenging (51). These patients need more attention, and further studies in the following areas may be helpful, including the healthcare utilisation patterns (especially emergency department attendance and hospitalisation), the type of care during their end of life, the supportive system for them, their health literacy about liver disease and alcohol use, and their view and preference in terms of end of life care.

Our study has several limitations and the findings should be interpreted with caution. First, it is an observational study, so the causal relationship between contributory causes of death and hospital death cannot be established. Second, some findings related to socioeconomic characteristics from the data may be subject to ecological fallacy, which may not perfectly represent the real association between individuals within those groups. Third, the death certificate data lack some important information in, e.g. lifestyle, disease history, treatment course, hospital types, or healthcare utilisation patterns. Some of the above clinical information can be enriched via linking to other routinely collected data, such as the Clinical Practice Research Datalink (52) and/or the Hospital Episodes Statistics database (53). Furthermore, the proportion of hospital death and its trend are highly related to hospital bed capacity (54, 55). If the number of deaths increased but the provision of hospital didn't grow, the proportion of hospital death could decrease year by year regardless of patients' choice, socio-demographic factors, or clinical characteristics. In addition, studies using mortality statistics are at risk of certification bias (56). The comorbidities of patients are not always recorded in death certification data, and there is probably coding variation across different health care settings.

Also, since our study population was those who died from liver disease, we therefore excluded the patients with liver disease but otherwise who died from a non-liver-related cause (57) or died without cause of death recorded. Finally, the choice of ICD-10 codes and the application of surrogate codes (e.g. G93.4 for hepatic encephalopathy, K65 for spontaneous bacterial peritonitis) could cause bias.

Conclusions

The annual deaths from liver disease increased steadily between 2001 and 2014 in England. Alcoholic liver disease was the most common underlying cause of death. Two-thirds of people dying from liver disease eventually died in hospitals. Patients with sepsis, hepatorenal syndrome, or peritonitis were associated with high hospital death, which warrants further investigation. The reasons for the disproportionately low hospital death in patients with alcohol related disorders need to be explored. Last but not least, there is a dire need for prevention strategies as well as end of life care services to prevent and tackle harms from liver disease.

List of abbreviations

UK: United Kingdom

ONS: Office for National Statistics

ICD-10: the 10th edition of International Classification of Diseases

IMD: Indices of Multiple Deprivation

LSOA: lower layer super output area

PR: prevalence ratio

Declarations

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Ethics approval and consent to participate

Following ONS procedures, a Data Access Agreement was signed, with requisites for data management and protection. In addition, as required, all researchers accessing the data (JKP, IJH, WG) were individually assessed and approved by ONS. This study was based on fully anonymised records and therefore no ethical approval was required according to the Information Commissioner's Office guidelines, ONS procedures and those of the King's College London Research Ethics Committee.

Consent for publication

Not applicable

Availability of data and material

According to the data agreement we signed with the ONS, we are not allowed to share our data. The access to the data would need special approvals from the ONS.

Competing interests

The authors declare that they have no potential competing interests.

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Authors' contributions

WG and IJH were co-PIs. JKP and WG designed the study. JKP performed the analysis and WG provided statistic supervision. JKP wrote the first draft with input from WG. IJH provided clinical and scientific input. All authors reviewed the findings, agreed the interpretation, and had full access to all data in the

study, and read and approved the final version. The corresponding author (JKP) had final responsibility for the decision to submit for publication.

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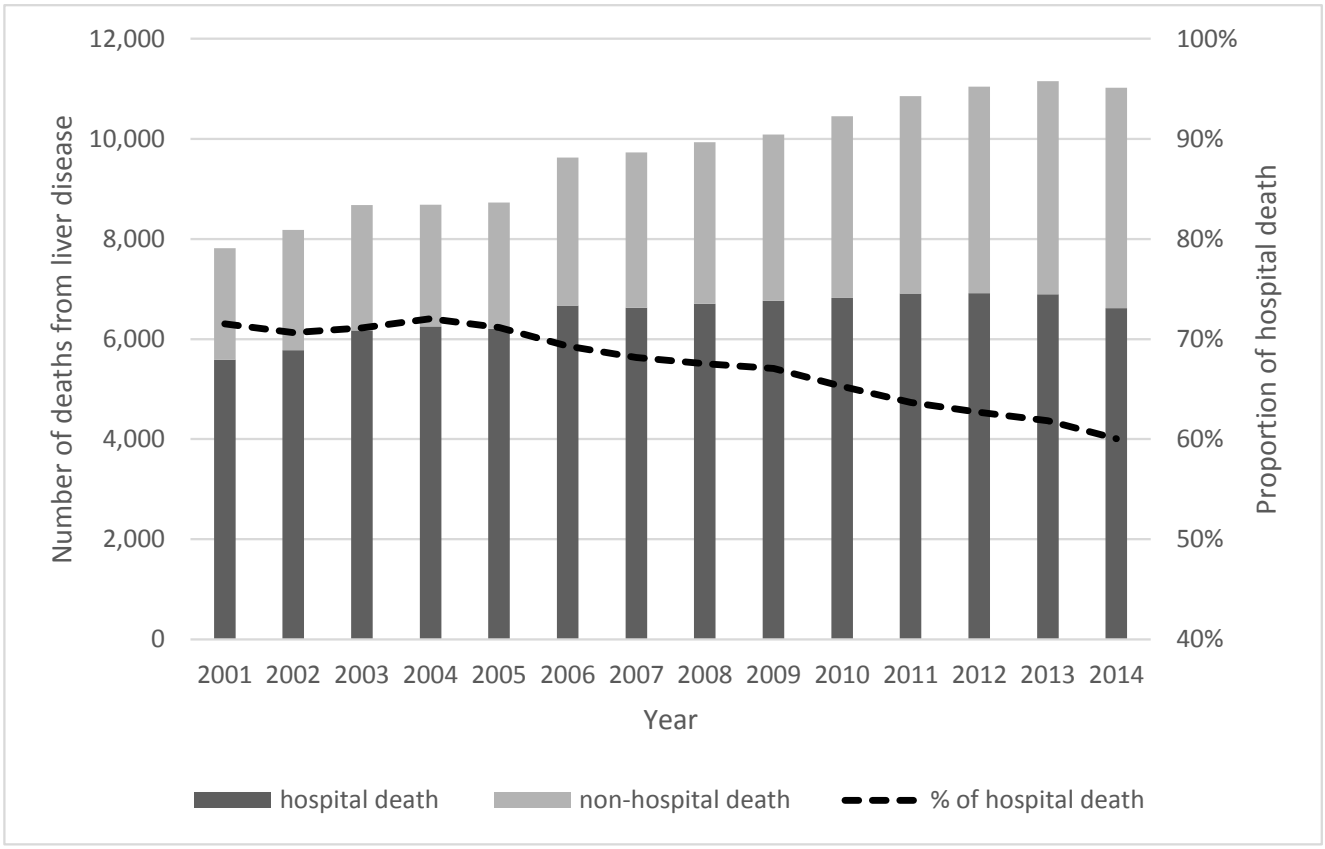
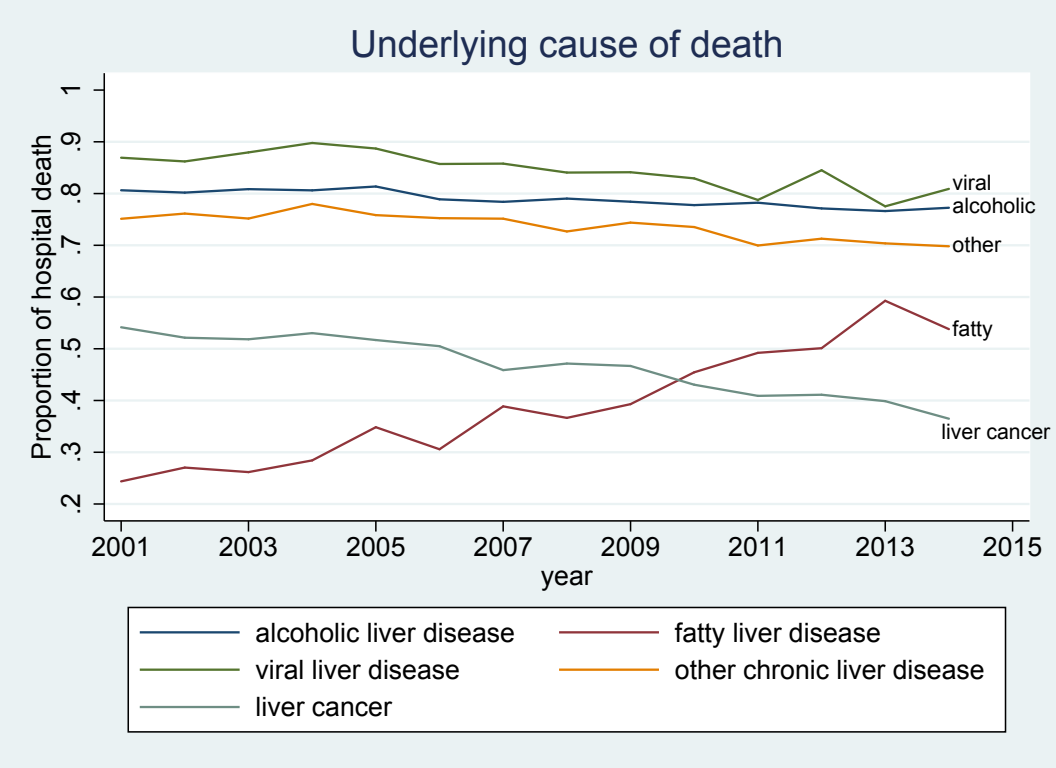
Table 1–3

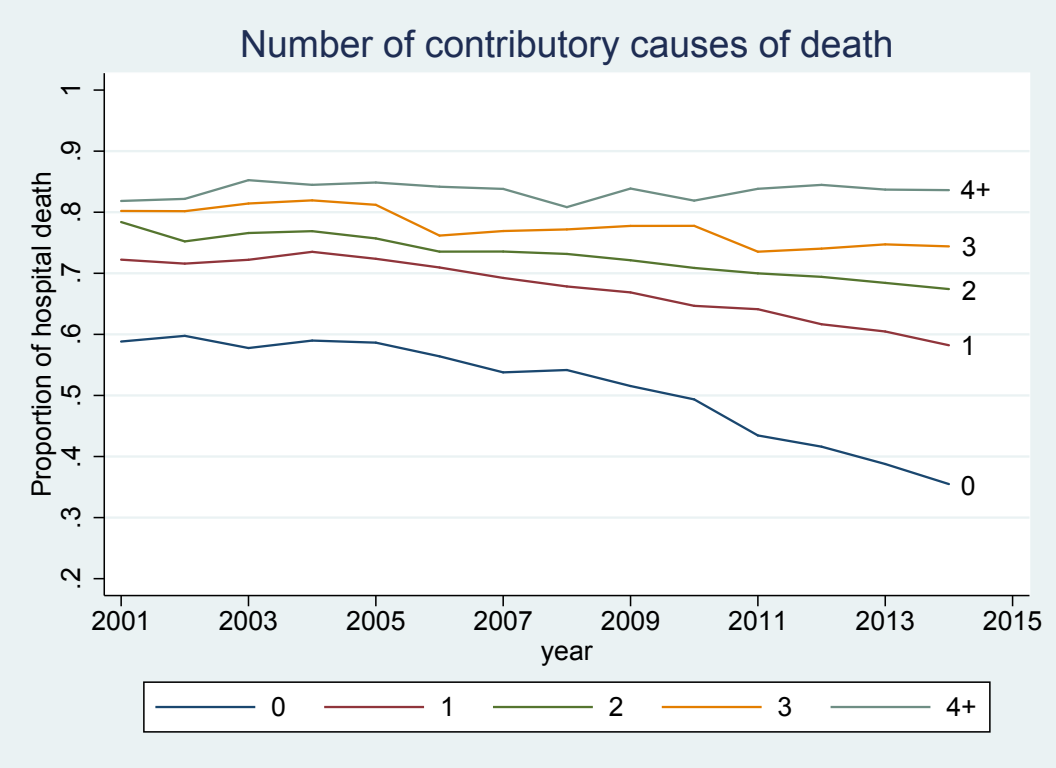
(uploaded as additional files)

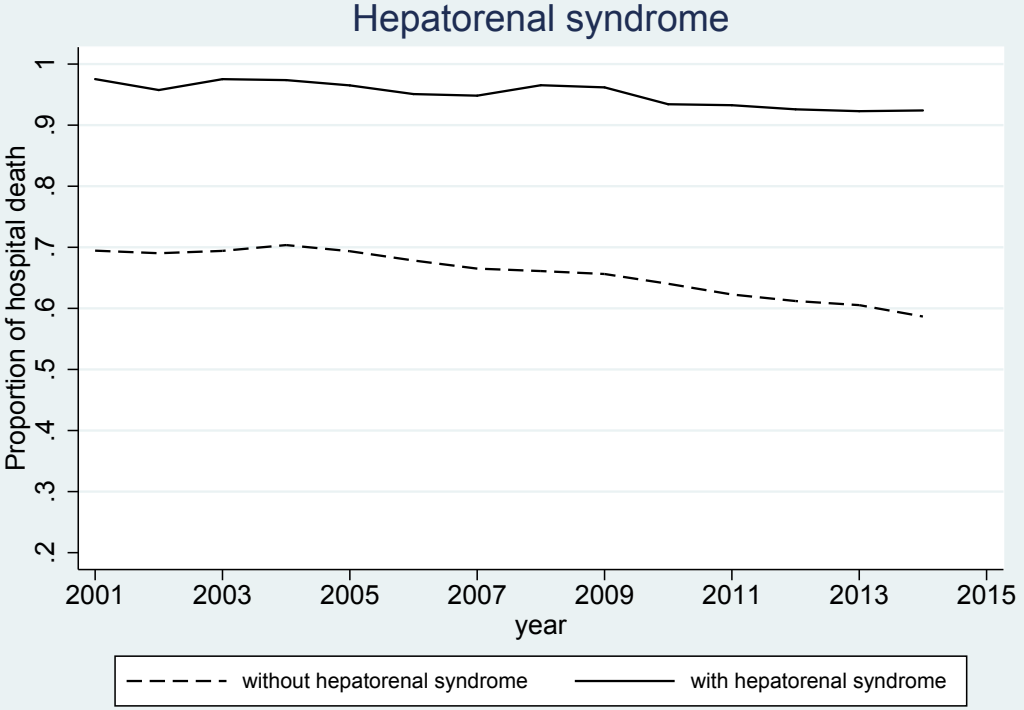
Figure 1. Number of deaths and proportion of hospital death in decedents who died from liver disease, England 2001–2014

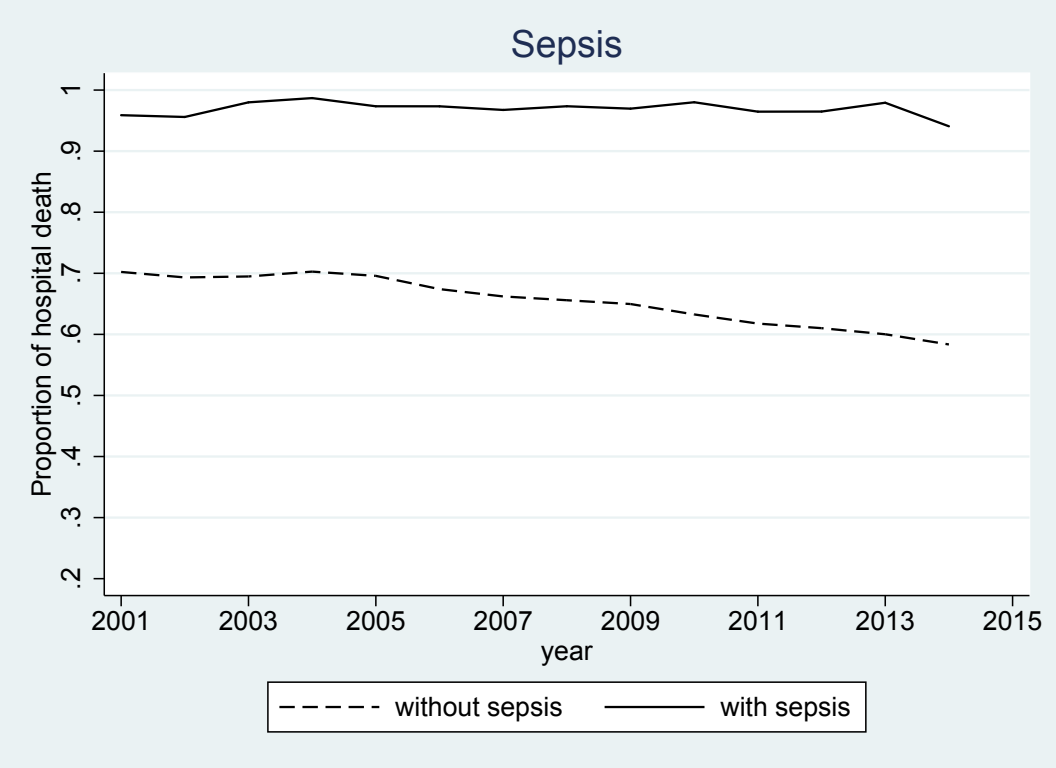
Figure 2. Time trends of proportion of hospital deaths for liver disease stratified by underlying cause of death, number of contributory causes of death, and the presence of several contributory causes of death (hepatorenal syndrome, sepsis, peritonitis, and alcohol related disorder given the underlying cause of death was alcoholic liver disease).

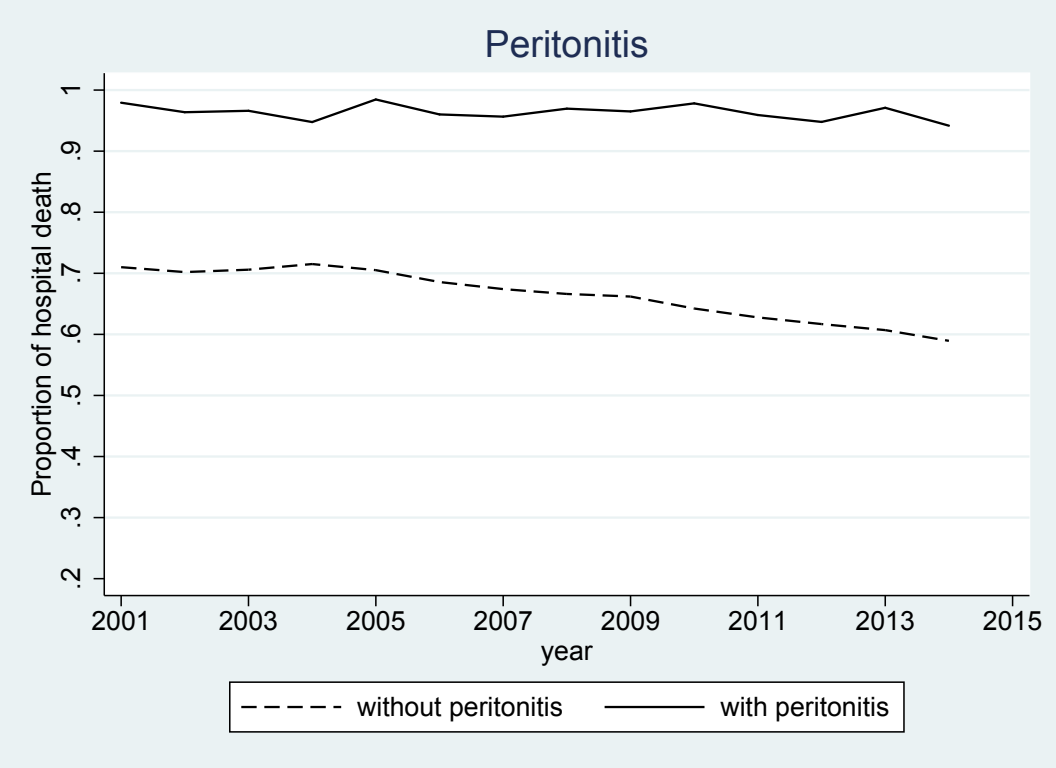

12,000
10,000
8,000
6,000
4,000
2,000
0
Number of deaths from liver disease
100%
90%
80%
70%
60%
50%
40%
Proportion of hospital death
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Year
hospital death
non-hospital death
% of hospital death


Underlying cause of death
Proportion of hospital death
.2
.3
.4
.5
.6
.7
.8
.9
1
2001
2003
2005
2007
2009
2011
2013
2015
year
viral
alcoholic
other
fatty
liver cancer
alcoholic liver disease
fatty liver disease
viral liver disease
other chronic liver disease
liver cancer


Number of contributory causes of death
Proportion of hospital death
.2
.3
.4
.5
.6
.7
.8
.9
1
2001
2003
2005
2007
2009
2011
2013
2015
year
4+
3
2
1
0
0
1
2
3
4+


Hepatorenal syndrome
Proportion of hospital death
.2
.3
.4
.5
.6
.7
.8
.9
1
2001
2003
2005
2007
2009
2011
2013
2015
year
without hepatorenal syndrome
with hepatorenal syndrome


Sepsis
Proportion of hospital death
.2
.3
.4
.5
.6
.7
.8
.9
1
2001
2003
2005
2007
2009
2011
2013
2015
year
without sepsis
with sepsis


Peritonitis
Proportion of hospital death
.2
.3
.4
.5
.6
.7
.8
.9
1
2001
2003
2005
2007
2009
2011
2013
2015
year
without peritonitis
with peritonitis

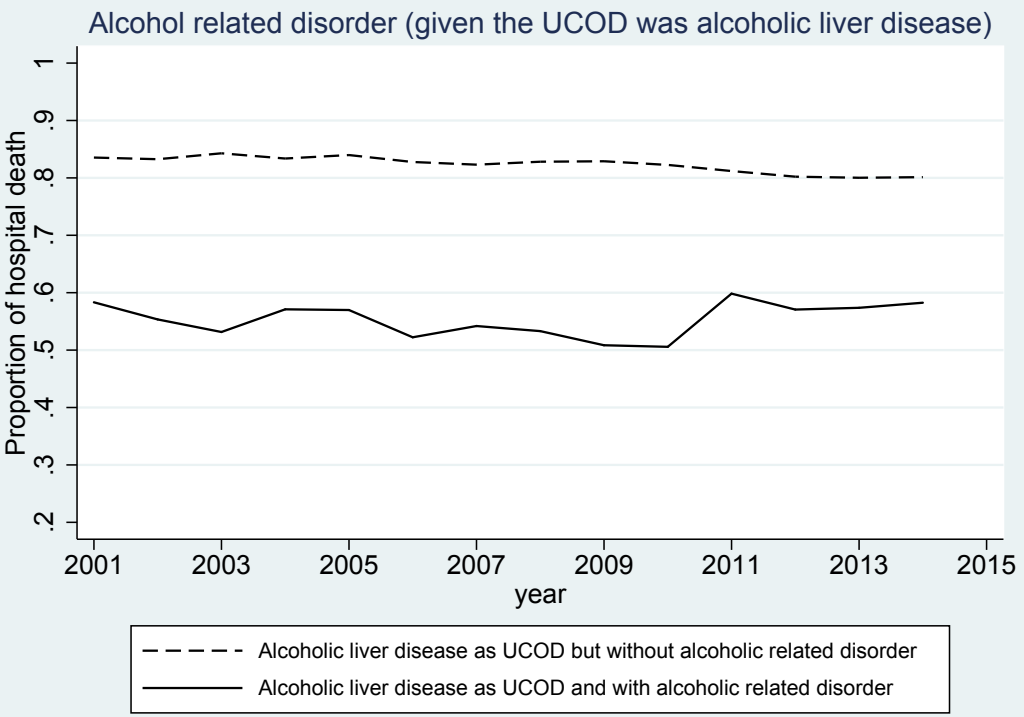

Alcohol related disorder (given the UCOD was alcoholic liver disease)
Proportion of hospital death
.2
.3
.4
.5
.6
.7
.8
.9
1
2001
2003
2005
2007
2009
2011
2013
2015
year
Alcoholic liver disease as UCOD but without alcoholic related disorder
Alcoholic liver disease as UCOD and with alcoholic related disorder

Table 1. Socioeconomic characteristics of the adult patients who died from liver disease in England, 2001–2014 (N=135,953)

Characteristics	Place of death						
	Total (N=135953)	Hospital (N=90921)	Non-hospital (N=45032)				p-value
			Home (N=29786)	Hospice (N=7462)	Care home (N=5866)	Others (N=1918)	
	N (column %)	N (row %)	N (row %)	N (row %)	N (row %)	N (row %)	
Age of death in years							
mean (SD)	62.8 (14.6)	61.8 (14.4)	61.7 (14.3)	69.1 (12.7)	77.2 (11.8)	58.2 (16.4)	<0.001
range	18–109	18–104	18–109	18–100	22–104	18–98	
18-34	2946 (2.2)	2125 (72.1)	630 (21.4)	86 (2.9)	12 (0.4)	93 (3.2)	<0.001
35-44	12759 (9.4)	9045 (70.9)	3057 (24.0)	227 (1.8)	67 (0.5)	363 (2.8)	
45-54	26259 (19.3)	18680 (71.1)	6220 (23.7)	701 (2.7)	202 (0.8)	456 (1.7)	
55-64	31758 (23.4)	22238 (70.0)	7156 (22.5)	1425 (4.5)	586 (1.8)	353 (1.1)	
65-74	28942 (21.3)	19151 (66.2)	6279 (21.7)	2148 (7.4)	1119 (3.9)	245 (0.8)	
75-84	23907 (17.6)	14424 (60.3)	4885 (20.4)	2184 (9.1)	2145 (9.0)	269 (1.1)	
85+	9382 (6.9)	5258 (56.0)	1559 (16.6)	691 (7.4)	1735 (18.5)	139 (1.5)	
Sex							<0.001
Male	83676 (61.5)	55417 (66.3)	19677 (23.5)	4375 (5.2)	2978 (3.6)	1229 (1.5)	
Female	52277 (38.5)	35504 (67.9)	10109 (19.3)	3087 (5.9)	2888 (5.5)	689 (1.3)	
Marital status							<0.001
Married	58028 (42.7)	39211 (67.6)	12583 (21.7)	4120 (7.1)	1657 (2.9)	457 (0.8)	
Single	24263 (17.8)	16450 (67.8)	5770 (23.8)	762 (3.1)	757 (3.1)	524 (2.2)	
Widowed or widow from civil partnership	24198 (17.8)	15230 (62.9)	4292 (17.7)	1619 (6.7)	2667 (11.0)	390 (1.6)	
Divorced, separated, or dissolved civil partnership	27469 (20.2)	18827 (68.5)	6506 (23.7)	923 (3.4)	735 (2.7)	478 (1.7)	
Unknown or not stated	1995 (1.5)	1203 (60.3)	635 (31.8)	38 (1.9)	50 (2.5)	69 (3.5)	
Year of death							<0.001
2001-2004	33352 (24.5)	23790 (71.3)	6588 (19.8)	1330 (4.0)	1139 (3.4)	505 (1.5)	
2005-2008	38010 (28.0)	26212 (69.0)	7957 (20.9)	1974 (5.2)	1376 (3.6)	491 (1.3)	
2009-2014	64591 (47.5)	40919 (63.4)	15241 (23.6)	4158 (6.4)	3351 (5.2)	922 (1.4)	
Index of multiple deprivation quintile							<0.001
1 (most deprived)	41009 (30.2)	28425 (69.3)	9057 (22.1)	1547 (3.8)	1308 (3.2)	672 (1.6)	
2	29842 (22.0)	20214 (67.7)	6474 (21.7)	1462 (4.9)	1245 (4.2)	447 (1.5)	
3	25093 (18.5)	16625 (66.3)	5451 (21.7)	1491 (5.9)	1187 (4.7)	339 (1.4)	
4	21837 (16.1)	14085 (64.5)	4834 (22.1)	1486 (6.8)	1162 (5.3)	270 (1.2)	
5 (least deprived)	18172 (13.4)	11572 (63.7)	3970 (21.8)	1476 (8.1)	964 (5.3)	190 (1.0)	
Settlement							<0.001
Urban	115150 (84.7)	77645 (67.4)	24822 (21.6)	6240 (5.4)	4799 (4.2)	1644 (1.4)	
Rural	20803 (15.3)	13276 (63.8)	4964 (23.9)	1222 (5.9)	1067 (5.1)	274 (1.3)	
Residential region							<0.001
London	17882 (13.2)	12185 (68.1)	3692 (20.6)	1249 (7.0)	494 (2.8)	262 (1.5)	
South East	19305 (14.2)	12514 (64.8)	4112 (21.3)	1503 (7.8)	910 (4.7)	266 (1.4)	
South West	12597 (9.3)	8106 (64.3)	2928 (23.2)	758 (6.0)	631 (5.0)	174 (1.4)	
East of England	12056 (8.9)	7746 (64.3)	2882 (23.9)	647 (5.4)	619 (5.1)	162 (1.3)	
East Midlands	11261 (8.3)	7477 (66.4)	2381 (21.1)	453 (4.0)	781 (6.9)	169 (1.5)	
West Midlands	15694 (11.5)	10921 (69.6)	3328 (21.2)	700 (4.7)	547 (3.5)	198 (1.3)	
Yorkshire and The Humber	13758 (10.1)	9223 (67.0)	2874 (20.9)	784 (5.7)	678 (4.9)	199 (1.4)	
North East	8756 (6.4)	5926 (67.7)	2013 (23.0)	267 (3.0)	421 (4.8)	129 (1.5)	
North West	24644 (18.1)	16823 (68.3)	5576 (22.6)	1101 (4.5)	785 (3.2)	359 (1.5)	

Table 2. Clinical characteristics of the adult patients who died from liver disease in England, 2001–2014 (N=135,953)

Characteristics	Place of death			
	Total (column %)	Hospital (row %)	Non-hospital (row %)	p-value
Underlying cause of death				<0.001
Alcoholic liver disease	56065 (41.2)	44216 (78.9)	11849 (21.1)	
Fatty liver disease	4071 (3.0)	1686 (41.4)	2385 (58.6)	
Viral liver disease	2795 (2.1)	2355 (84.3)	440 (15.7)	
Other chronic liver disease	33536 (24.7)	24730 (73.7)	8806 (26.3)	
Liver cancer	39486 (29.0)	17934 (45.4)	21552 (54.6)	
Number of contributory causes of death				<0.001
0	33804 (24.9)	17131 (50.7)	16673 (49.3)	
1	44154 (32.5)	29860 (67.6)	14294 (32.4)	
2	32193 (23.7)	23368 (72.6)	8825 (27.4)	
3	15257 (11.2)	11753 (77.0)	3504 (23.0)	
4+	10545 (7.8)	8809 (83.5)	1736 (16.5)	
Contributory cause of death				
Influenza and Pneumonia				<0.001
With	17304 (12.7)	14070 (81.3)	3234 (18.7)	
Without	118649 (87.3)	76851 (64.8)	41798 (35.2)	
Esophageal varices (EV)				0.129
With	9529 (7.0)	6440 (67.6)	3089 (32.4)	
Without	126424 (93.0)	84481 (66.8)	41943 (33.2)	
Cardiovascular disease				0.471
With	9429 (6.9)	6274 (66.5)	3155 (33.5)	
Without	126524 (93.1)	84647 (66.9)	41877 (33.1)	
Cancer (non-liver cancer or metastatic cancer)				<0.001
With	9111 (6.7)	4274 (46.9)	4837 (53.1)	
Without	126842 (93.3)	86647 (68.3)	40195 (31.7)	
Diabetes mellitus				0.655
With	8075 (5.9)	5382 (66.7)	2693 (33.3)	
Without	127878 (94.1)	85539 (66.9)	42339 (33.1)	
Alcohol related disorders				<0.001
With	7671 (5.6)	4323 (56.4)	3348 (43.6)	
Without	128282 (94.4)	86598 (67.5)	41684 (32.5)	
Sepsis				<0.001
With	7564 (5.6)	7335 (97.0)	229 (3.0)	
Without	128389 (94.4)	83586 (65.1)	44803 (34.9)	
Hepatorenal syndrome (HRS)				<0.001
With	7048 (5.2)	6709 (95.2)	339 (4.8)	
Without	128905 (94.8)	84212 (65.3)	44693 (34.7)	
Renal disease				<0.001
With	4923 (3.6)	4258 (86.5)	665 (13.5)	
Without	131030 (96.4)	86663 (66.1)	44367 (33.9)	
Pulmonary disease				<0.001
With	3709 (2.7)	2586 (69.7)	1123 (30.3)	
Without	132244 (97.3)	88335 (66.8)	43909 (33.2)	
Peritonitis				<0.001
With	3562 (2.6)	3429 (96.3)	133 (3.7)	
Without	132391 (97.4)	87492 (66.1)	44899 (33.9)	
Neurological conditions				<0.001
With	2537 (1.9)	1837 (72.4)	700 (27.6)	
Without	133416 (98.1)	89084 (66.8)	44332 (33.2)	
Peptic ulcer disease				<0.001
With	1108 (0.8)	817 (73.7)	291 (26.3)	
Without	134845 (99.2)	90104 (66.8)	44741 (33.2)	
Dementia				<0.001
With	891 (0.7)	473 (53.1)	418 (46.9)	
Without	135062 (99.3)	90448 (67.0)	44614 (33.0)	
Ascites				0.001
With	811 (0.6)	587 (72.4)	224 (27.6)	
Without	135142 (99.4)	90334 (66.8)	44808 (33.2)	
Encephalopathy				<0.001
With	472 (0.3)	404 (85.6)	68 (14.4)	
Without	135481 (99.7)	90517 (66.8)	44964 (33.2)	
Hepatopulmonary syndrome (HPS)				<0.001
With	459 (0.3)	371 (80.8)	88 (19.2)	
Without	135494 (99.7)	90550 (66.8)	44944 (33.2)	
Connective tissue disorder				<0.001
With	412 (0.3)	310 (75.2)	102 (24.8)	
Without	135541 (99.7)	90611 (66.9)	44930 (33.1)	

Table 3. Factors associated with hospital deaths* (versus non-hospital deaths) in adult patients who died from liver disease in England, 2001–2014 (N=135,953)

Variable	Value	Unadjusted PR (95% CI)	Adjusted PR (95% CI)
Age of death (ref: 18–44)	45–54	1.00 (0.99–1.01)	1.00 (0.98–1.01)
	55–64	0.98 (0.97–1.00)	1.02 (1.01–1.03)
	65–74	0.93 (0.92–0.94)	1.06 (1.04–1.07)
	75+	0.83 (0.82–0.84)	1.06 (1.04–1.07)
Sex (ref: Male)	Female	1.03 (1.02–1.03)	1.05 (1.04–1.05)
Marital status (ref: married)	Single	1.00 (0.99–1.01)	0.93 (0.92–0.94)
	Widowed or widow from civil partnership	0.93 (0.92–0.94)	0.95 (0.94–0.97)
	Divorced, separated, or dissolved civil partnership	1.01 (1.00–1.02)	0.92 (0.92–0.93)
	Unknown or not stated	0.89 (0.86–0.93)	0.83 (0.81–0.86)
Year of death (ref: 2001–2004)	2005–2008	0.97 (0.96–0.98)	0.97 (0.96–0.98)
	2009–2014	0.89 (0.88–0.90)	0.91 (0.90–0.92)
IMD quintile (ref: 1, most deprived)	2	0.98 (0.97–0.99)	1.00 (0.99–1.01)
	3	0.96 (0.95–0.97)	1.00 (0.99–1.01)
	4	0.93 (0.92–0.94)	0.98 (0.97–0.99)
	5 (least deprived)	0.92 (0.91–0.93)	0.98 (0.97–0.99)
Settlement (ref: Urban)	Rural	0.95 (0.94–0.96)	0.99 (0.98–1.00)
Residential region (ref: London)	South East	0.95 (0.94–0.97)	0.95 (0.94–0.96)
	South West	0.94 (0.93–0.96)	0.95 (0.93–0.96)
	East of England	0.94 (0.93–0.96)	0.95 (0.94–0.97)
	East Midlands	0.97 (0.96–0.99)	0.96 (0.94–0.97)
	West Midlands	1.02 (1.01–1.04)	0.98 (0.96–0.99)
	Yorkshire and The Humber	0.98 (0.97–1.00)	0.97 (0.95–0.98)
	North East	0.99 (0.98–1.01)	0.98 (0.96–1.00)
	North West	1.00 (0.99–1.02)	0.98 (0.96–0.99)
Underlying cause of death (ref: alcoholic liver disease)	Fatty liver disease	0.53 (0.51–0.54)	0.52 (0.50–0.54)
	Viral liver disease	1.07 (1.05–1.09)	0.96 (0.95–0.98)
	Other chronic liver disease	0.94 (0.93–0.94)	0.85 (0.84–0.86)
	Liver cancer	0.58 (0.57–0.58)	0.61 (0.60–0.61)
Number of contributory causes of death (ref: 0)	1	1.33 (1.32–1.35)	1.20 (1.18–1.21)
	2	1.43 (1.41–1.45)	1.24 (1.22–1.26)
	3	1.52 (1.50–1.54)	1.32 (1.31–1.34)
	4+	1.65 (1.63–1.67)	1.45 (1.42–1.47)
Contributory cause of death			

Sepsis	With vs without	1.49 (1.48–1.50)	1.24 (1.23–1.25)
Hepatorenal syndrome	With vs without	1.46 (1.45–1.47)	1.22 (1.21–1.22)
Peritonitis	With vs without	1.46 (1.45–1.47)	1.18 (1.17–1.20)
Renal disease	With vs without	1.30 (1.29–1.32)	1.11 (1.10–1.13)
Influenza and Pneumonia	With vs without	1.26 (1.24–1.27)	1.08 (1.07–1.09)
Hepatopulmonary syndrome	With vs without	1.21 (1.16–1.26)	1.07 (1.03–1.12)
Encephalopathy	With vs without	1.28 (1.23–1.33)	1.06 (1.02–1.10)
Neurological conditions	With vs without	1.08 (1.06–1.11)	1.00 (0.98–1.02)
Connective tissue disease	With vs without	1.13 (1.06–1.19)	0.99 (0.94–1.05)
Pulmonary disease	With vs without	1.04 (1.02–1.07)	0.94 (0.92–0.96)
Peptic ulcer disease	With vs without	1.10 (1.07–1.14)	0.93 (0.90–0.96)
Ascites	With vs without	1.08 (1.04–1.13)	0.85 (0.81–0.88)
Cancer (non-liver or metastatic cancer)	With vs without	0.69 (0.67–0.70)	0.80 (0.78–0.81)
Dementia	With vs without	0.79 (0.75–0.84)	0.77 (0.73–0.82)
Alcohol related disorders	With vs without	0.83 (0.82–0.85)	0.67 (0.66–0.69)

* The results were derived from modified Poisson regression models, adjusting the listed variables. Only those were statistically significant in bivariate analysis were included in the multivariate analysis.